REMARKS

Claims 30, 31, 36 and 37 were pending and stand rejected. The Examiner has made a number of rejections. Claims 49-56 have been added. The only remaining rejection is as follows:

(1) Claims 30, 31, 36 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent 5,316,931.

Applicants believe that the following remarks traverse the Examiner's rejection of the claims. These remarks are presented in the same order as they appear above.

I. THE CLAIMS ARE NOT ANTICIPATED

The Examiner has rejected Claims 30, 31, 36 and 37 under 35 U.S.C. 102(e) as anticipated by U.S. Patent 5,316,931. The Applicants respectfully disagree.

In the Office Action (p.3), the Examiner points to a number of areas in the '931 Patent and argues 1) "a foreign peptide . . . was inserted in a site in a viral nucleic acid sequence coding for a viral coat protein, and 2) that "The foreign nucleic acid insert is free of flanking direct repeats." With respect to the latter, the Examiner is asked to note that the claims speak of the **site** of the insert being free of flanking direct repeats - not whether the **insert** is free of flanking direct repeats. With respect to the former, it is respectfully submitted that the Examiner is reading more into the '931 Patent than is really there. Both of these points are discussed in detail below.

As a general approach, applicants wish to remind the Examiner that Patent law requires the Examiner to determine what is taught "as a whole" in the '931 Patent. To this end, the Examiner is asked to re-read the text of the specification carefully in light of the comments and quotes set forth below. Secondly, the Examiner is asked to examine the data (i.e. what was achieved and what was NOT achieved) of the '931 Patent. These '931 results are discussed below in the context of the experimental achievements of the present application.

A. The Text Of The '931 Patent Teaches Insertion In The Context Of The First Embodiment - Where Non-Native Coat Protein Coding Sequences Are Used

The Examiner is asked to first re-read the last paragraph of the "Background" section where two problems in the art are described:

> "However, none of these viral vectors have been capable of systemic spread in the plant . . ." (col. 3, lines 24-25)
>
> and
>
> ". . . the prior art viral vectors . . . are not stable for the maintenance of non-viral foreign genes." (col. 3, lines 28-29).

These two problems are addressed in the '931 as set forth in the "Summary of the Invention" section of the '931 Patent. The Examiner will find that four (4) embodiments are taught. In the first embodiment, the "native coat protein coding sequence has been deleted" (col. 3, lines 50-51) and replaced with a non-native coat protein coding sequence, and "Non-native (foreign) nucleic acid sequences may be inserted adjacent the native plant viral subgenomic promoter" (col. 3, lines 66-68) or adjacent the non-native promoter. In the second embodiment, the nucleic acid sequence encoding the coat protein is placed "adjacent one of the non-native coat proteins." In the third embodiment, "one or more non-native subgenomic promoters have been inserted" and non-native nucleic acid sequences can be inserted "adjacent the non-native subgenomic plant viral promoters." (col. 4, lines 12-25). The fourth embodiment is a modification of the third embodiment, wherein "the native coat protein coding sequence is replaced by a non-native coat protein coding sequence." (col. 4, lines 28-29).

Three technical points should be clear from the re-reading of this entire section. First, the insertion of non-native coding sequences into coat protein coding sequences is not even mentioned. Second, the flanking sequences of the site of the insert are not discussed (accept to say what promoter might be used). Third, there are embodiments wherein coding sequence for the native coat protein are deleted.

In the "Detailed Description" section, these embodiments are discussed again. It is here - for the first time - that the specification of the '931 Patent says anything about inserting non-native coding sequences into coat protein coding sequences. The '931

specification notes, as a variation on the first embodiment (where the native coat protein gene is deleted and replaced with a non-native coat protein coding sequence), the following:

> "Alternatively, the coat protein gene may be **inactivated** by insertion of the non-native nucleic acid sequence within it, such that a fusion protein is produced." (col. 5, lines 66-68 and col. 6, line 1) (emphasis added).

The Examiner is asked to take note that the '931 Patent does not discuss the impact of the insertion of non-native nucleic acid sequences within the coat protein gene other than to say the coat protein gene is "inactivated." Further understanding of the term "inactivated" comes from the following text of the '931 specification:

> "If it is deleted or otherwise **inactivated,** a non-native coat protein gene is inserted under control of one of the non-native subgenomic promoters . . . The non-native coat protein is capable of encapsidating the recombinant plant viral nucleic acid to produce a recombinant plant virus. . . . The coat protein is involved in the systemic infection of the plant host." (col. 9, lines 1-13) (emphasis added)

This language is revealing. When combined with the above-quoted language from column 5, it is clear that the '931 Patent introduces the non-native coat protein coding sequences in the context of either i) deletion of the native coat protein coding sequences (which is embodiment one as written), or ii) inactivation of the native coat protein coding sequence by insertion of foreign sequences into the native coat protein coding sequences (which is the "alternative" to embodiment one discussed at col. 5). Said another way, the '931 Patent teaches that the insertion of foreign sequences into the native coat protein coding sequences is compensated for by a second coat protein coding sequence (non-native) in order that the coat protein be operative for systemic infection.

By contrast, the present invention is concerned with insertions that are not deleterious to the function of the native coat protein. In this regard, the Examiner is asked to contrast the above-quoted '931 Patent language (wherein the native coat protein gene is said to be "inactivated") with the language of the applicants' specification:

> ". . . the insertions are made such that the additions are exposed on either the internal or external surface of the virus and such that assembly of the coat protein subunits and the infectivity of the virus are not abolished." (see the present specification, p. 9, bottom paragraph)

The present specification teaches ways to avoid a deleterious impact from the insertion of sequences into the coat protein coding sequences:

> ". . . to prevent the introduction of repeated sequences which may facilitate reversion, pairs of complementary oligonucleotides were synthesized in which the sequence encoding the heterologous amino acids are flanked by sequences present in wild type [virus] . . . Such a strategy not only ensures that the heterologous sequences are inserted at the optimal site and that the inserts are not flanked by direct repeats but also ensures that no CPMV-specific sequences are deleted, a fact believed to be important in enabling virus particles to assemble . . ." (see the present specification, p. 22, middle of the page)

The Examiner is asked to take note of the new claims wherein language (tracking the above-quoted language) has been included for embodiments where "no coat protein coding sequences are deleted" (Claim 49) and "where assembly of the coat protein is not abolished" (Claim 53). The Examiner is also requested to take note of new Claim 50 which specifies an embodiment using the above-quoted method (oligos encoding the foreign peptide "flanked by sequences present in wild type virus"). Finally, the Examiner is asked to note pending Claim 31 which specifies an embodiment wherein "the insert is an *addition* to said coat protein."

B. The '931 Patent Experiments Teach Success Only With Embodiments That Do Not Involve Insertion Into The Native Coat Protein Coding Sequences

As noted above, the language regarding insertion of foreign genes into the native coat protein coding sequences is an "alternative" or variation on embodiment one of the '931 Patent. Most importantly, *there is no experimental work in the '931 Patent where this variation is tested!*

The Examiner is directed to the Examples beginning at column 20. In "Comparative Example 1" a CAT gene is used as the foreign gene and it is inserted "behind a TMV subgenomic RNA promoter between the 30K and coat protein genes of TMV." This is NOT a case of insertion *within* coat protein genes. Interestingly, the '931 Patent reports LOSS of the insert (i.e. the same problem seen in the prior art and discussed in the Background section as quoted above). The '931 Patent speculates that the loss might be due to homologous recombination given the fact that the deletion occurred between repeated sequences (Col. 24,

lines, 23-40). Applicants which to stress that this speculation is not in the context of an insertion of foreign coding sequences into native coat protein coding sequences.

In "Comparative Example 2" the CAT gene placement is moved to "between the coat protein gene and the nontranslated 3' region of TMV." (Col. 24, lines 45-47). Again, this is NOT a case of insertion *within* coat protein genes. Interestingly, the '931 Patent reports that this "replicated poorly" (Col. 24, lines 64-65) and "no systemic symptoms appeared" (Col. 25, lines 2-3) when used to inoculate plants. On the other hand, loss of the insert was apparently not observed (Col. 25, lines 9-15).

"Comparative Example 3" is written (at least partly) in the present tense and is (apparently to some degree) prophetic. In any event, the example teaches that the coat protein coding sequence is deleted (Col. 25, line 25) and the foreign sequence (the NPTII gene) is placed "adjacent the coat protein promoter." (Col. 25, line 51). Again, this is NOT a case of insertion *within* coat protein genes.

"Comparative Example 4" involves constructs as described in Comparative Examples 1 and 3 - thus, NOT involving insertion *within* coat protein genes. While systemic spread of the vector was observed, a loss of the NPTII gene was indicated (Co. 26, lines 9-14).

The examples in the "Preferred Embodiments" begin at Col. 26. The constructs used are shown in Figure 1, wherein one can see that the native coat protein coding sequences were either just deleted, or replaced with a non-native coat protein coding sequence. Again, there is no case of insertion *within* coat protein genes. Better retention of the inserted foreign gene is reported and the '931 Patent speculates:

> "It was hypothesized that with the previously reported constructs, foreign inserts were deleted due to recombination between repeated subgenomic promoter sequences. With TBD4 and TBN62, *such repeated sequences were reduced* by employing heterologous subgenomic mRNA promoters." (Col. 28, lines 42-47, emphasis added).

The Examiner is respectfully asked a simple question at this point: is the "reducing" of repeated sequences by the use of heterologous subgenomic promoters enough to anticipate a claim requiring that the insert site be "free" of flanking repeat sequences? Clearly not. Moreover, Claim 30 specifies that the insert site be within the coat protein coding sequences. The use of heterologous subgenomic promoters in the '931 Patent says nothing about repeats within the coat protein coding sequences. This is why Applicants submit the Examiner's

statements (i.e. the two quoted at the outset of this response) are not supported and involve the Examiner "reading in" features that are simply not present in the '931 Patent.

Moreover, while better retention was achieved, the '931 Patent still reports that NPTII sequences were eventually lost and the '931 Patent offers no explanation:

> "The time of loss of these sequences varied between after the first passage (12-24 days) and the third passage (36-47 days). The reason for the occurrence of deletions in the NPTII sequence of TBN62 is not known." (Col. 29, lines 10-14).

Thus, the problem of loss of the insert is not solved by these constructs.

In contrast to the above-discussed results of the '931 Patent, the present application contains examples 1) involving insertion *within* coat protein coding sequences, where 2) the insert is stable. Example 2 notes the following in this regard:

> "To confirm that the insert had been retained, the products derived from samples taken from plants after initial inoculation and after three serial passages were cloned [and sequenced] . . . All the clones in both instances contained the sequence corresponding to viral RNA which retained the inserted sequence intact. . . . Analysis of RNA extracted . . . supported the conclusion that the new constructs are genetically stable, no evidence of reversion being found after 10 serial passages."

This data shows that the embodiments of the present invention involving a) insertion *within* coat protein coding sequences, b) no loss of coat protein coding sequences, and c) insert sites free of flanking repeat sequences produced better results than that described in the prior art.

Importantly, these elements are NOT found in the cited art. While the '931 Patent teach that the use of heterologous promoters may "reduce" repeat sequences, such a teaching cannot anticipate claims which specify a insert site i) within the coat protein coding sequences, that ii) is free of repeat sequences. With regard to the embodiment involving no loss of coat protein coding sequences, the '931 Patent teaches the opposite: either deleting the native coat protein coding sequences or "inactivating" the gene.

When the precise claim limitations at issue are carefully studied *in the context of where the insertion site is*, it is clear that the '931 Patent cannot anticipate. The Examiner is not free to piece together an anticipation argument by grabbing disparate bits of information from the '931 Patent and assembling them out of context. For this reason, the rejection must be withdrawn.

CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that these grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 617.252.3353.

Dated: June 17, 2003

Peter G. Carroll
Registration No. 32,837

MEDLEN & CARROLL, LLP
220 Montgomery Street, Suite 2200
San Francisco, California 94104

APPENDIX I
CLEAN VERSION OF THE ENTIRE SET OF PENDING CLAIMS PURSUANT TO 37 CFR § 1.121 (c)(3)

The Following is a version of the claims pursuant to 37 C.F.R. § 1.121(c)(3) showing a clean version of the pending claims.

30. A method for producing plant virus particles comprising: a) providing i) plant viral nucleic acid comprising nucleic acid which codes for a coat protein, ii) a foreign nucleotide sequence coding for a foreign peptide; b) modifying said plant viral nucleic acid by inserting said foreign nucleotide sequence coding for a foreign peptide at a site within said plant viral nucleic acid which codes for the coat protein so as to create modified viral nucleic acid comprising an insert, wherein said site is free from direct sequence repeats flanking said insert; c) infecting plant material selected from the group consisting of plants, plant tissue, plant cells and protoplasts with said modified viral nucleic acid to produce assembled particles of a modified virus; and d) harvesting assembled particles of the modified virus from said plant material.

31. The method according to claim 30, in which the insert is an addition to said coat protein.

36. The method according to claim 30, in which the foreign nucleotide sequence is inserted by i) selecting two different restriction enzyme sites in the plant viral nucleic acid; ii) cutting the plant viral nucleic acid using the corresponding restriction enzymes; and iii) inserting into the cut viral nucleic acid a pair of complementary oligonucleotides which encode the foreign peptide and which terminate in ends compatible with the restriction enzyme cutting sites.

37. A method according to claim 36, in which in the complementary oligonucleotides, the sequence encoding the foreign peptide is flanked by plant virus-specific sequences so that the foreign nucleotide sequence is inserted as an addition to the plant viral nucleic acid.

49. A method for producing plant virus particles comprising: a) providing i) plant viral nucleic acid comprising nucleic acid which codes for a coat protein, ii) a foreign nucleotide sequence coding for a foreign peptide; b) modifying said plant viral nucleic acid by inserting said foreign nucleotide sequence coding for a foreign peptide at a site within said plant viral nucleic acid which codes for the coat protein so as to create modified viral nucleic acid comprising an insert, wherein no coat protein coding sequences are deleted, and wherein said site is free from direct sequence repeats flanking said insert; c) infecting plant material selected from the group consisting of plants, plant tissue, plant cells and protoplasts with said modified viral nucleic acid to produce assembled particles of a modified virus; and d) harvesting assembled particles of the modified virus from said plant material.

50. The method of Claim 49, in which the foreign nucleotide sequence is inserted by i) selecting two different restriction enzyme sites in the plant viral nucleic acid; ii) cutting the plant viral nucleic acid using the corresponding restriction enzymes; and iii) inserting into the cut viral nucleic acid a pair of complementary oligonucleotides which encode the foreign peptide flanked by sequences present in wild type virus which terminate in ends compatible with the restriction enzyme cutting sites.

51. The method of Claim 49, wherein said foreign nucleotide sequence encodes a portion of a mammalian viral protein.

52. The method of Claim 51, wherein said portion is between six and twenty-one amino acids in length.

53. A method for producing plant virus particles comprising: a) providing i) plant viral nucleic acid comprising nucleic acid which codes for a coat protein, ii) a foreign nucleotide sequence coding for a foreign peptide; b) modifying said plant viral nucleic acid by inserting

said foreign nucleotide sequence coding for a foreign peptide at a site within said plant viral nucleic acid which codes for the coat protein so as to create modified viral nucleic acid comprising an insert, where assembly of the coat protein is not abolished; c) infecting plant material selected from the group consisting of plants, plant tissue, plant cells and protoplasts with said modified viral nucleic acid to produce assembled particles of a modified virus; and d) harvesting assembled particles of the modified virus from said plant material.

54. The method of Claim 53, in which the foreign nucleotide sequence is inserted by i) selecting two different restriction enzyme sites in the plant viral nucleic acid; ii) cutting the plant viral nucleic acid using the corresponding restriction enzymes; and iii) inserting into the cut viral nucleic acid a pair of complementary oligonucleotides which encode the foreign peptide and which terminate in ends compatible with the restriction enzyme cutting sites.

55. The method of Claim 53, wherein said foreign nucleotide sequence encodes a portion of a mammalian viral protein.

56. The method of Claim 55, wherein said portion is between six and twenty-one amino acids in length.